Court File No.: 05-CV-303001PD2

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

CANWEST MEDIAWORKS INC.

Applicant

and

ATTORNEY GENERAL OF CANADA

Respondent

REPLY AFFIDAVIT OF JOEL LEXCHIN

I, **JOEL LEXCHIN**, of the City of Toronto, in the Province of Ontario, solemnly AFFIRM:

1. I have provided evidence in this matter on behalf of the Attorney General of Canada in an affidavit sworn June 30th, 2006. My qualifications to provide this evidence, which includes, among other things, evidence on pharmaceutical policy and drug therapy, and pharmaceutical promotion, are fully described therein.

2. In this affidavit I will respond to the evidence of Drs. Julie Donohue, Richard Dolinar and Don Fulgosi and Professor Michael J. Trebilcock. Where I have quoted the opinions and findings of other authors in my response to these affidavits, they are widely accepted as experts in the matters on which they have written and their statements reflect my own opinion as well. Where I refer to

sources that are not attached, the references for them are set out in a Bibliography attached as Exhibit 1 to this affidavit.

A. RESPONSE TO THE AFFIDAVIT OF DR. JULIE DONOHUE

1) Brand and Class Effect

3. In paragraphs 34 to 40 Donohue cites several studies that found that DTCA was not associated with a change in prescription choice within a drug class although prescribing for the entire class did increase. It seems clear that if the volume of prescribing for an entire class increases then the prescribing for the individual drugs in the class must also increase. Therefore, if a product has, for example a 50% share of a class then it should have half of all of the increased prescribing of that class. It would make rational economic sense for a company with a significant market share to engage in DTCA even if its overall share of the market did not increase. There is also some evidence from a European study of promotion for fungal toenail infection, that I cited in my original affidavit, that contradicts what Donohue claims.[1] That study found that an "awareness campaign" around fungal toenail infection was associated with both an increase in new prescriptions and the market share of the company's specific antifungal agent (increased prescribing volume during the period of the campaign from 6.50 prescriptions per 1000 person years (95% CI 6.33 to 6.66) to 15.2 (95% CI 13.5 to 16.9)).

4. If a drug is the first in its class then DTCA would also obviously have a beneficial effect since there would not be any competitors. An example of

this can be found in a study I cited in my previous affidavit that showed that a marketing campaign for sumatriptan, the first antimigraine drug in its class, was associated with a marked increase in sales.[1]

5. In paragraph 40 Donohue states that a study by Schneeweiss and colleagues[2] found that physician characteristics mattered more in the prescribing of COX-2 medications than did patient characteristics. She uses this finding to state that "an important implication of the lack of a market share effect for DTCA is that physician preferences matter a great deal for prescription drugs." However, she neglects to include a key sentence in the paper. The authors also say "physician prescribing preferences ... also reflect the extent to which patients increasingly request selective COX-2 inhibitors instead of nonselective NSAIDs." A key reason why patients will request a particular drug or class of drugs will be their exposure to DTCA.

2) <u>DTCA Effects on Prescribing</u>

6. In paragraph 30 of her affidavit Dr. Donohue makes the statement that direct-to-consumer advertising (DTCA) of prescription drugs is likely to lead to the increased use of medications in undertreated conditions and cites a number of such conditions such as diabetes, hypertension, hyperlipidemia and mental disorders. In paragraphs 44 to 55 she returns to this theme of suboptimal prescribing practices.

7. Claims of undertreatment rest largely on the assumption that the results of premarketing clinical trials can be generalized to the wider population with the same condition, i.e., that the same benefit to harm ratio will apply to the wider population as was seen in the patients who participated in the premarketing trials. This concept of generalization is termed external validity.

8. External validity has been subject to an extensive review by Rothwell in Lancet in 2005.[3] He lists a wide variety of issues that may affect external validity including: setting of the clinical trial; selection of patients; characteristics of randomized patients; differences between the trial protocol and routine practice; outcome measures and follow up; and adverse effects of treatments. Of particular importance he notes "Drug licensing bodies, such as the US Food and Drug Administration, do not require evidence that a drug has a clinically useful treatment effect, or a trial population that is representative of routine clinical practice."

9. While he does mention that for conditions such as hypertension results of clinical trials are usually generalizable this is not the situation for many other interventions. He concludes that some trials have good external validity but many do not "especially some of those done by the pharmaceutical industry." The Rothwell review in Lancet in 2005 is attached as Exhibit 2 to this affidavit.

10. The vast majority of the clinical trials now undertaken are funded by the drug companies. Seventy percent of the $5.6 billion (US) spent in 2002 on clinical trials in the United States came from the biomedical industry.[4] A review of studies looking at the outcome of clinical trials as a function of the funding source showed that overwhelmingly when trials are sponsored by pharmaceutical companies they are much more likely to show positive results than if funding for these trials comes from other sources.[5]

11. In summary, in my opinion the problem with the external validity of premarketing clinical trials along with the bias that results from the industry funding of the majority of these trials means that for many diseases it is impossible to determine what the magnitude of the problem of undertreatment is and whether it is more significant than overtreatment.

12. Even where there is evidence of undertreatment it is far from clear that DTCA would lead to appropriate treatment. The vast majority of DTCA spending goes to new medications. However the safety profile of these medications is not well delineated. In Ontario, when rofecoxib (Vioxx®) and celecoxib (Celebrex®) were introduced there was a 41% rise in the use of nonsteroidal anti-inflammatories in the province of Ontario accompanied by a 10% increase in hospitalization rates for upper gastrointestinal bleeding.[6] In the 2 – 4 years that bromfenac, dexfenfluramine and mibefradil, all drugs that were withdrawn for safety reasons, were on the US market in the mid to late 1990s 6.4 million people were exposed to them.[7] Twenty percent of new drugs approved in

the US will either acquire a new black box warning or be withdrawn over a 25 year period and half of the withdrawals will occur in the first 2 years that the products are on the market.[8]

13. The most recent prominent example of safety problems occurring with a new treatment is the case of rosiglitazone (Avandia®) a heavily prescribed treatment for Type II diabetes. Recent research has strongly suggested that this drug leads to a significant increase in the risk for a myocardial infarction and a borderline-significant increase in mortality from cardiovascular causes.[9] While there is still debate over the safety profile of this drug, two prominent researchers have editorialized in the New England Journal of Medicine that "the rationale for prescribing rosiglitazone at this time is unclear."[10]

14. In paragraph 45, Donohue cites a study by Shrank and colleagues[11] as evidence that underprescribing is a more significant issue than overprescribing to support her contention that overall an increased use of prescription drugs brought about by DTCA would be a positive move. Shrank and colleagues identified 76 indicators of underprescribing for 30 acute and chronic conditions that are the leading causes of illness, death and utilization of health care but only 19 indicators of overprescribing so the fact that they concluded that underprescribing was a more significant problem was not unexpected.

15. Their choice of what conditions to assess can be questioned. For instance in looking at overprescribing they did not list the use of antibiotics for viral infections, cough and cold remedies for viral upper respiratory tract infections or the use of nonsteroidal anti-inflammatory agents in the absence of inflammation. In reaching conclusions about what constitutes over and underprescribing they only considered conditions in isolation. Many patients, particularly the elderly, suffer from multiple medicals problems and what might be appropriate prescribing were the patient to have that condition in isolation might be overprescribing in the context of many medical problems. Even for single conditions some of their indicators can be questioned. As one example, they deem it appropriate for anyone under age 75 who has elevated cholesterol uncontrolled with diet to need medication despite the fact that using pharmacotherapy as primary prevention has never been shown to reduce morbidity or mortality.[12]

16. Therefore, in my opinion, Donohue is overstating the significance of this study and it cannot be used to definitively state that undertreatment is more important than overtreatment.

17. In paragraph 51 Donohue refers to my evidence regarding the limitations of her study in Medical Care.[13] While I accept that she used a time trend analysis and that she looked at patients suffering from major depression as a subgroup, it remains my opinion that her study still has limitations that may be significant. Although she uses adjustments for secular trends in the treatment of

depression, without a proper control group, which she lacks, she cannot be sure that she has controlled for all of the relevant factors. The main reason for using a control group is to try and account for unknown factors that may affect the findings.

18. Further, she bases her assumptions about the rate at which the effects of DTCA diminish over time on the results of a study by Ling and coworkers.[14] Ling and colleagues only looked at a single class of drugs, the H2 blockers, and the data that they used for DTCA spending only covered the period up to the end of the second quarter of 2000. At that point, the ratio of print to television advertising was different than it currently is. In 2000 television advertising accounted for 65% of total DTCA spending[15] whereas now it is just below 75%[16] and as well overall DTCA has gone up by more than 50%.[17] Therefore, Donohue's assumptions about how rapidly the effects of DTCA diminish may no longer be accurate.

3) <u>Physician Prescribing Practices and Patient Outcomes</u>

19. In paragraphs 56-58 Donohue criticizes the study by Mintzes and colleagues.[18] Donohue's criticisms of the study are valid but as one of the authors of the study I do not believe that they are of sufficient magnitude to change the overall conclusion that Mintzes reached. Mintzes' study has been widely recognized as making a significant contribution to knowledge about the effects of DTCA as shown by the frequency with which it has been cited (33 times as of November 16, 2007 according to the Web of Science database) and

the confirmation of its findings about the possible negative effects on prescribing by the results in Kravitz.

20. In paragraphs 61-65 Donohue discusses the study by Kravitz and colleagues.[19] She concludes that the study tells us about the nature of patients' influence over doctors' prescribing but little about the effects of DTCA because the characteristics of patients who respond to DTCA are poorly understood.

21. In my expert opinion her criticism does not invalidate the findings in the Kravitz study but does suggest that further research in this area needs to be done to clarify the characteristics of patients who respond to DTCA and to determine whether the findings about the effects of DTCA on prescribing for depression and adjustment disorder can be generalized to other conditions. None-the-less, because Kravitz used the most robust kind of methodology, a randomized controlled trial, his findings provide the strongest evidence that DTCA can lead to overprescribing.

B. RESPONSE TO THE AFFIDAVIT OF DR. DON FULGOSI

22. In paragraph 18 of his affidavit Dr. Don Fulgosi states that my suggestion about limiting the number of patients who are exposed to new drugs amounts to an extension of a clinical trial and that there should be informed consent and some formal method for choosing the patients. Fulgosi's statement represents a serious misunderstanding of how new drugs should be introduced into a doctor's practice.

23. When drugs are tested in clinical trials patients are carefully chosen and the results of those trials can only accurately be applied to similar patients when a new drug is on the market. Therefore, until more is known about the drug, if it is not going to be used in this particular group of patients, it behooves doctors to be sure that there is no other equivalent, but better known, product that is available for their patients. If doctors choose to prescribe the new product then they need to carefully monitor their patients for any untoward effects from this new drug. This method of dealing with new drugs is simply good medical practice. Finally, whenever doctors prescribe for patients they should outline the expected benefits and possible risks. To repeat my earlier evidence, DTCA violates the appropriate ways in which new drugs should be introduced because DTCA has been shown to lead to very rapid uptake of new drugs, which can lead to more harm than benefit. This outcome, whereby the benefit to harm ratio becomes negative, is because knowledge of the safety profile of new drugs is necessarily limited because of the inherent limitations of clinical trials that I discussed earlier in this affidavit.

24. In paragraph 22 Fulgosi says that if there are increased risks of adverse drug reactions arising from rapid uptake of newly-approved drugs that this risk can be dealt with by requiring special warnings. However, there is a body of literature that indicates that including warnings with drugs does not influence prescribing behaviour.[20-22]

25. In paragraphs 27-32 Fulgosi states that DTCA can lead to patients bringing up new drugs that lead to a discussion with the doctor about various treatment options. Fulgosi ignores findings from the United States that a substantial fraction of patients who request a drug from their doctors will simply go to another doctor if their request is denied by the first doctor they visit.[23-25] Furthermore, he ignores the evidence cited in my previous affidavit from New Zealand that shows that only 28% of general practitioners (GPs) who responded to a survey indicated that DTCA did not interfere with the doctor-patient relationship.[26] Even if one assumes that there was a biased response to the survey, 50% of New Zealand GPs responded and therefore the overwhelming majority of non-responders would have to hold a contrary opinion for the results of this survey to be reversed.

26. In paragraphs 29-31 Fulgosi displays a lack of understanding of the value of new drugs and how GPs use medications. Most new drugs do not represent any significant therapeutic breakthrough as is shown by Canadian, European and French data.[27-30] In his own field of psychiatry, recent research shows that except in a few specific cases the newer heavily promoted class of second generation antipsychotics are no more effective or safer than the first generation.[31] Meta-analyses have found that in primary care treatment of depression there is no difference in efficacy between the newer selective serotonin reuptake inhibitors and the older tricyclic group of drugs, although the withdrawal rate due to side effects tended to be slightly higher with the tricyclic antidepressants.[32, 33] Finally, contrary to what Fulgosi asserts, GPs do not need

to know about the thousands of drugs that are on the Canadian market. Older research shows that nearly all of the prescribing that the average GP does comes from a basket of between 150 to 250 drugs.[34] Although I am not aware of any more recent work in this area, in my opinion as a practicing doctor there are no reasons to expect that current practice is any different.

27. In paragraph 32 Fulgosi claims that DTC advertisements offer a fair balance between the benefits and risks of medications and that they have an educational value for patients. Two analyses of television DTC advertisements both show that the ads lack fair balance and have limited educational value.[35, 36] In general these analyses found that television ads provided limited information about the causes of a disease or who may be at risk. Only a minority of the ads informed consumers that the advertised drugs might not work for everyone and the majority of the ads did not provide any information about risk factors or symptoms that might raise awareness among undiagnosed individuals.

28. In paragraphs 35-44 Fulgosi criticizes my interpretation of three studies that I cited in my original affidavit in support of my contention that DTCA can lead to inappropriate prescribing.[18, 19, 26] Fulgosi's affidavit does not present any evidence that he has had any formal training in clinical epidemiology and his criticisms need to be seen in that light. Moreover, he does not present any evidence to show that DTCA leads to improved prescribing.

29. In paragraphs 65-84 Fulgosi discusses the question of whether or not DTCA leads to the medicalization of normal life. In this discussion he ignores evidence of how DTCA can expand the spectrum of diseases so that minor symptoms become an illness that needs pharmacotherapy. A few examples can be used to illustrate this point.

30. Woloshin and Schwartz describe how GlaxoSmithKline used advertising to exaggerate the prevalence and seriousness of restless leg syndrome.[37] Lexchin discusses how Pfizer expanded the market for Viagra® for erectile dysfunction by using ads with a man who says he doesn't want to fail even one time.[38] In Canada, Hoffmann-La Roche markets Orlistat ® a drug for weight loss only indicated for people with a body mass index of 30 or greater (or people with a body mass index of 27 and additional risk factors for cardiovascular disease), that is, people with extreme obesity. However, in 2005 the company ran a series of reminder ads featuring a fictional woman named "Julie" with the message "what would you do with a few pounds less?"[39]

C. RESPONSE TO THE AFFIDAVIT OF DR. RICHARD DOLINAR

31. In paragraphs 27 to 49 Dr. Richard Dolinar discusses the educational value of DTCA. I have already pointed out in my response to the affidavit of Fulgosi that content analysis of broadcast advertisements shows that they have little educational value and that they lack "fair balance".

32. Dolinar also draws on his personal experience as a physician regarding the educational value of DTCA. Although DTCA is restricted in Canada I have been exposed to many such ads through viewing American television. My opinion as a physician in practice for 30 years is that these ads are seriously lacking in educational value. The ads usually use idyllic scenery to suggest that everyone will benefit from the medication and present side effects in a monotonic voice again with the idyllic scenery to distract from the verbal message. In my opinion as a practicing doctor the contrast between the visual and verbal messages will have the effect of minimizing the verbal information about risks that is being given.

33. In paragraph 47 Dolinar points out that patients use the internet to get information about medications. He does not point out that there is a fundamental difference between accessing information on the web, which is an active process, and watching television commercials which is a passive process. When patients go on the internet looking for information they have multiple sites to choose from and they can go from site to site and get different opinions about a specific product and also look for alternative forms of treatment. These types of options are not available to people who watch commercials.

34. Dolinar has also not looked at the literature that analyzes the content of web sites sponsored by pharmaceutical companies. Graber and Weckmann looked at company web sites for antidepressants and concluded "[t]he information about drugs for treating depression on pharmaceutical

company websites aimed at consumers is limited and makes it difficult for consumers to compare drugs."[40] Similarly, information on company web sites for drugs for erectile dysfunction was found to be "superficial and aimed primarily at consumers. It is largely promotional and provides only limited information needed to effectively compare treatment options."[41]

D. RESPONSE TO THE AFFIDAVIT OF PROFESSOR MICHAEL TREBILCOCK

35. In paragraph 31 of his affidavit Professor Michael Trebilcock states that the main impediment to regulating DTCA is that the regulating authority has not been given adequate resources. His conclusion is that if this problem was alleviated that DTCA could be properly controlled and therefore would not need to be banned.

36. As far as industry self regulation is concerned the issue is not lack of resources but a lack of will to set and enforce standards that will appropriately control DTCA. Trebilcock has not demonstrated that even with adequate resources pharmaceutical promotion can be adequately controlled. Trebilcock believes that since DTCA is highly visible that it should be easy to regulate. However, as an expert in this area, I have not come across a single jurisdiction anywhere in the world that has been able to adequately regulate pharmaceutical advertisements in medical journals, also a highly visible form of advertising, such that they are not misleading. My conclusions are backed up my multiple analyses of different aspects of journal ads in a variety of countries including Australia,[42]

Canada,[43-45] Finland,[46] Spain,[47] Sweden,[48] United Kingdom,[44, 49] and the United States.[44, 48, 50-54]

AFFIRMED before me at the City of Toronto, in the Province of Ontario this day of December, 2007.

(Commissioner for Taking Affidavits)

JOEL LEXCHIN